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Preferential Action of Mexiletine on Central Common Pathway of Reentrant Ventricular Tachycardia

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Objectives. **The action of mexiletine on diseased myocardium was assessed in reentrant ventricular tachycardia (VT).**

Background. **Whether class Ib antiarrhythmic agents exert a preferential action on the central common pathway of reentrant ventricular tachycardia has not yet been studied in humans.**

Methods. **In 10 consecutive patients (7 with a previous myocardial infarction, 3 with nonischemic disease), VT was induced and entrained with rapid pacing. The orthodromic conduction time was measured from stimulus to the entrained electrogram at the exit from the presumed central common pathway (i.e., the earliest site of activation). Mexiletine at 125 to 250 mg was administered intravenously, and when VT with the same configuration was induced, the study was repeated. The action of mexiletine on the central common pathway was assessed from the changes in VT cycle length and orthodromic conduction time. The effects on QRS complex duration, local conduction time between the exit and the pacing site and duration of the local electrogram were compared between normal and diseased myocardium.**

Results. **Mexiletine prolonged the VT cycle length in all patients, from (mean ± SD) 316 ± 30 to 360 ± 64 ms (mean change 20 ± 7%, $p < 0.001$); during entrainment of VT, the orthodromic conduction time was prolonged, from 306 ± 58 to 367 ± 89 ms (mean change 18 ± 9%, $p < 0.001$). These changes were highly correlated ($r = 0.95$, $p < 0.001$). QRS duration changed little (4 ± 3%), and local conduction time showed no change. The duration of the fragmented electrogram width was prolonged by mexiletine: from 146 ± 50 to 176 ± 56 ms (mean change 23 ± 8% during VT, $p < 0.001$). Only a slight change occurred in the effective refractory period, both at the pacing site and at the exit.**

Conclusions. **Mexiletine caused little change in conduction time in normal myocardium but prolonged VT cycle length, orthodromic conduction time and duration of the local electrogram at the earliest site of activation of VT. From these findings, a preferential action of mexiletine on diseased myocardium was suggested but seemed to occur only at higher frequencies during tachycardia.**

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Procainamide has been shown to prolong the duration of the fractionated electrogram (1,2) and to preferentially depress conduction velocity within the reentrant circuit in human ventricular tachycardia (VT) (3). In contrast, the effects of mexiletine on the fractionated electrogram as well as on electrically abnormal myocardium have been reported to be negligible (1,4). These negative findings could be related to the absence of partial diastolic depolarization in the myocardium as the basis of slowed conduction (1,5) or, because the action of the drugs was studied during sinus rhythm, to fast dissociation from sodium channels (6–8). Another reason could be that sodium channel blockade and depression of conduction are relatively mild after mexiletine administration. One study (9) showed a preferential depression of conduction in the diseased myocardium by mexiletine but whether the site was related to the origin of VT was not defined.

In the present study, the action of mexiletine on the central common pathway and on the electrically abnormal electrogram were determined and compared with that in normal myocardium. Evidence of a preferential action of mexiletine on the slow pathway was revealed.

Methods

Patients. Ten consecutive patients (mean [±SD] age 56 ± 18 years, range 21 to 72; six men, four women) underwent serial drug testing for selection of antiarrhythmic agents for symptomatic monomorphic sustained VT. They fulfilled the following criteria for inclusion: 1) the same monomorphic sustained VT was inducible at the control study and after administration of mexiletine; 2) the site of VT origin was mapped by the endocardial catheter technique (10,11); and 3) VT was able to be entrained with rapid ventricular pacing at progressively shorter cycle lengths.

Old myocardial infarction (≥6 months after acute myocardial infarction) was found in seven patients in whom an occluded coronary artery to the infarction area was demon-

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Abbreviations and Acronyms
ECG = electrocardiogram
VT = ventricular tachycardia

strated by coronary arteriography. Left ventricular ejection fraction by left ventriculography was 0.43 ± 0.11. Two patients had idiopathic dilated cardiomyopathy, but left ventricular ejection fraction was >0.40. The remaining patient had undergone operation for double-outlet right ventricle 10 years previously and had normal left ventricular ejection fraction.

Electrophysiologic study. After a detailed explanation of the procedures, purpose and possible risks, written informed consent was obtained, and electrophysiologic studies were performed in the nonsedated and postabsorptive states, as reported earlier (11,12). Antiarrhythmic agents were discontinued 2 to 3 days before the control study, and no patient had been receiving amiodarone.

Three quadripolar electrode catheters with an interelectrode distance of 5 mm were introduced from the femoral vein and placed at the high right atrium, the His bundle recording region and the apex of the right ventricle. The electrode catheter in the right atrium was moved to the outflow tract of the right ventricle when necessary. Another catheter was placed in the left ventricle. They were used for stimulation and recording. Electrical stimuli were delivered at twice the late diastolic threshold and 2 ms of the width through a programmable stimulator (cardiac stimulator model BCO2, Fukuda Denshi Co., Tokyo, Japan).

Bipolar intracavitary electrograms were filtered at 30 to 500 Hz and recorded with three surface electrocardiographic (ECG) leads: I, II and V_1 on a strip chart at a paper speed of 100 or 200 mm/s (Mingograf 7, Siemens-Elema Co., Solna, Sweden). They were also stored on magnetic tape (cassette recorder model XR-5000, TEAC, Tokyo, Japan) and retrieved later for use on a thermal recorder (thermal recorder model RF-85 Fukuda Denshi Co.).

All induced arrhythmias were recorded on 12-lead ECGs and used for analysis of VT configuration.

Catheter mapping and rapid pacing of VT. Extensive endocardial mapping (10,11) was performed to localize the site of earliest activation during VT. The local electrogram at the site should precede the onset of the QRS complex of VT, and pace mapping at the site should result in QRS complex configurations identical or nearly identical to that of VT. The site of earliest activation of VT was presumed to be close to the exit from the central common pathway of the reentrant circuit, and the conduction time from the stimulus to the entrained electrogram at this site was assumed to represent orthodromic conduction, as described later.

Rapid pacing was then performed at a cycle length 10 to 20 ms shorter than that of the VT, and if the VT was entrained, rapid pacing was repeated at progressively shorter cycle lengths after a decrement in cycle length of 10-ms steps until interruption of VT (11,12). Rapid pacing was first attempted at the apex of the right ventricle, and when VT was unable to be entrained, rapid pacing was performed at the second or third site from the right ventricular outflow tract or from the left ventricle, respectively.

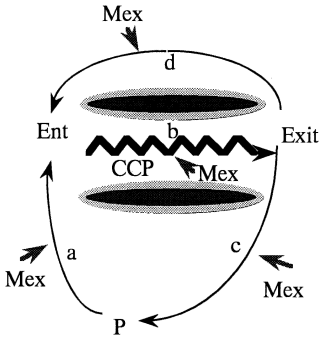

Figure 1. Schema of VT and conduction times. The reentrant circuit of VT is represented by the figure eight model. The entrance (Ent) to the central common pathway (CCP) may be unknown, but the exit (Exit) can be approximately determined as the site of the earliest activation by endocardial mapping. As long as the VT configuration remains unchanged, the exit is assumed to be spatially fixed. During VT, the wave fronts proceed to the outer loop with the conduction time (d) and the central common pathway with the conduction time (b). During transient entrainment, the orthodromic conduction time to the exit is the sum of the conduction time from the pacing site (P) to the entrance (undefined) (a) and then to the exit (b). The local conduction time (c) is defined as that from the exit to the pacing site. The drug-induced change in the central common path is reflected in the orthodromic conduction time (a + b) as well as in the VT cycle length (b + d). Mex = mexiletine.

According to the criteria of classical transient entrainment by earlier researchers (17,18), we used 1) demonstration of constant fusion during rapid pacing except for the last captured beat that occurred at the pacing rate in the surface ECG or intracavitary electrogram; 2) demonstration of progressive fusion at shorter paced cycle lengths; 3) interruption of VT with localized block to the site of the exit, followed by activation from a different direction with a shorter conduction time. In addition, another criterion was used when an electrode catheter was located within the central common pathway: 4) Rapid pacing at the site resulted in concealed entrainment (13–16).

Mexiletine administration. After the control study, mexiletine was administered intravenously at a dosage of 125 to 250 mg in 10 to 15 min. Electrode catheters were positioned at exactly the same sites during the administration of mexiletine, and the electrophysiologic variables were measured. A maintenance dose was not given, and plasma levels were not measured.

Rationale and data analysis. Because details of the reentrant circuit were not available, the reentrant circuit was assumed to be represented by a figure-eight model in which the central common pathway is separated by anatomic or functional block (Fig. 1).

In this model of VT, mexiletine acts on the slowly conduct-

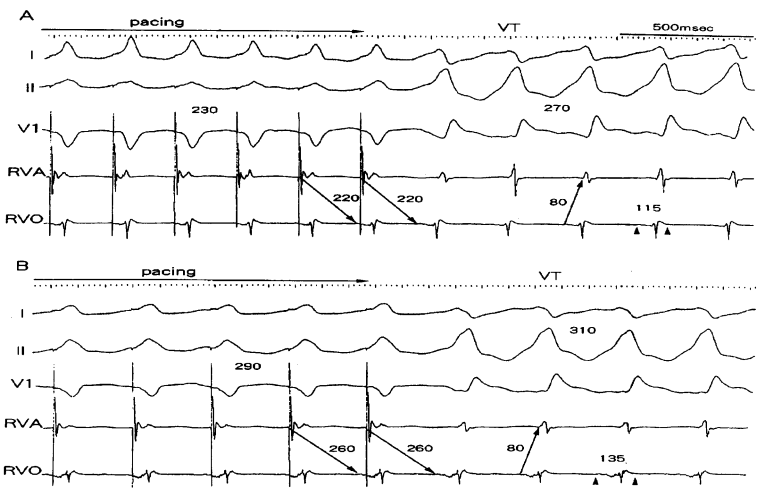

Figure 2. Changes in VT cycle length and orthodromic conduction time before and after mexiletine administration. Electrocardiographic tracings from a patient who developed monomorphic VT in the chronic stage after repair of double-outlet right ventricle. **A,** In the control state, VT had a cycle length of 270 ms, and rapid pacing from the apex of the right ventricle (RVA) was able to entrain the VT. The orthodromic conduction time was measured from the pacing stimulus to the earliest deflection of the local electrogram at the right ventricular outflow tract (RVO) as denoted by **arrows:** 220 ms. Rapid pacing was repeated at shorter cycle lengths after one decrement in steps of 10 ms, and VT was interrupted with rapid pacing at a critical cycle length (not shown). **B,** After mexiletine administration, the VT cycle length was prolonged to 310 ms, and rapid pacing from the same site was able to entrain and terminate the VT. The orthodromic conduction was prolonged to 260 ms. However, the time interval between the earliest deflection of the local electrogram at the right ventricular outflow tract to the pacing site (RVA) was unchanged: 80 ms before and after mexiletine. The width of the local electrogram at the right ventricular outflow tract was widened from 115 to 135 ms.

ing central common pathway and on the normal myocardium outside the slow pathway. The action on the central common pathway can be assessed from changes in the cycle length of VT (Fig. 1 [b + d]) and from the orthodromic conduction time (Fig. 1 [a + b]), which is measured from the pacing stimulus to the local electrogram at the exit, whereas the action on the normal myocardium can be assessed by analysis of changes in the local conduction time (Fig. 1 [c]), which is measured from the initial deflection of the electrogram at the exit to that of the pacing site during VT.

QRS duration was measured from the onset of the initial deflection to the terminal deflection and was used as an index of global intraventricular conduction. It was confirmed that the stimulus-local ventricular electrogram did not change.

The duration of the local electrogram was measured from the onset of the initial deflection to the terminal deflection in 3 consecutive beats at a paper speed of 100 mm/s, and the average was used as an index of localized myocardial conduction. A beat to beat variance was essentially not observed. The duration of the local electrogram was measured during sinus rhythm and VT.

The amplitude of the local electrogram was also measured as the peak to peak deflection and was measured at the exit (diseased myocardium) and at the pacing site (normal myocardium).

The effective refractory period was measured at the exit and at the pacing site (normal myocardium) as the longest coupling interval of the extrastimulus that failed to capture the myocardium at a basic cycle length of 400 ms. The effective refractory period was measured soon after termination of VT.

These variables were measured before and after mexiletine during VT identical in configuration to that at the control state. Ventricular tachycardia configuration was verified by a 12-lead ECG and the constant configuration and duration of the intracavitary electrograms. The measurements were repeated during reinduced VT and ended 15 to 30 min after completion of mexiletine administration.

Results are presented as mean value ± SD. The *t* test was used for paired samples and $p < 0.05$ was considered significant.

Results

Effect of mexiletine on VT cycle length and orthodromic conduction time. After mexiletine, the VT cycle length was prolonged (from 316 ± 30 to 360 ± 64 ms, mean change 20 ± 7%) and was significant ($p < 0.002$). Ventricular tachycardia induced after mexiletine showed a configuration nearly identical to that during the control state.

Rapid pacing during VT. All VTs were entrained with rapid pacing from the right ventricular apex in eight patients and from the right ventricular outflow tract in two and performed from the same site in before and after mexiletine (Fig. 2 and 3). As the paced cycle length decreased, the orthodromic conduction time showed a frequency-dependent prolongation in eight patients but was flat in two. In 9 of 10 patients, VT was terminated at a critical cycle length of 255 ± 35 and 301 ± 55 ms before and after mexiletine, respectively (mean change 22 ± 13%), with a significant prolongation ($p < 0.002$). The zone of entrainment (VT cycle length minus VT-interrupting paced cycle length) was unchanged: 66 ± 22 and 66 ± 44 ms before and after mexiletine, respectively. In the remaining patient, rapid pacing was stopped before termination.

The orthodromic conduction time that was obtained at the paced cycle length and was closest to the VT cycle length was 306 ± 58 ms in the control study and was prolonged to 367 ± 89 ms (mean change 18 ± 9%) after administration of mexiletine. The change in VT cycle length was highly corre-

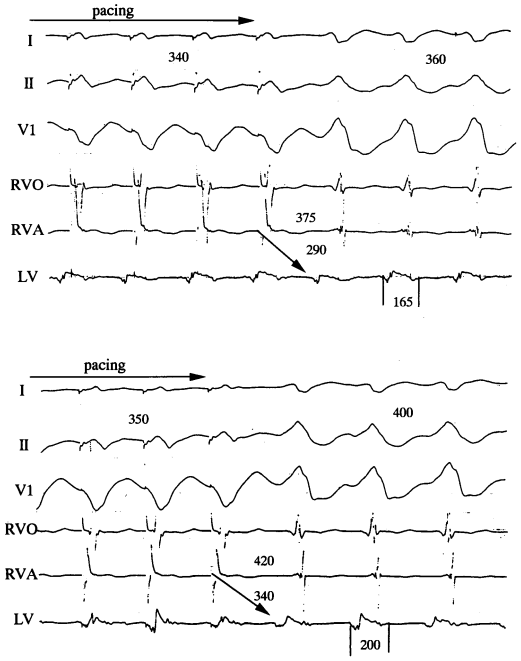

Figure 3. Effects of mexiletine on VT, conduction time and local electrogram. **Top,** During VT with a cycle length of 360 ms, rapid pacing was able to entrain VT, and the orthodromic conduction time was 290 ms. **Bottom,** After mexletine, the VT cycle length and the orthodromic conduction time were prolonged to 400 and 340 ms, respectively. The return cycle at the pacing site was 375 and 420 ms, respectively. LV = left ventricle; other abbreviations as in Figure 2.

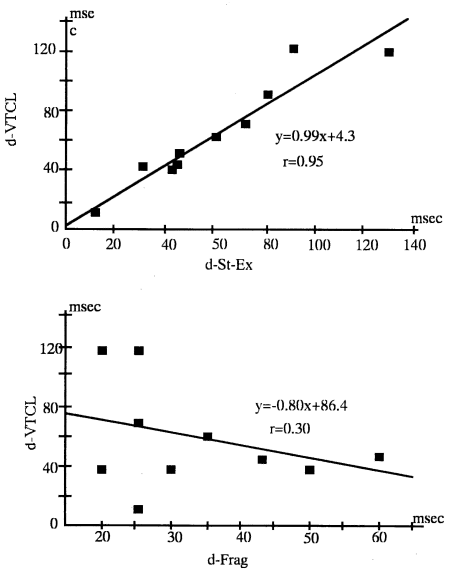

Figure 4. Relation between changes in VT cycle length (d-VTCL) and orthodromic conduction time (d-St-Ex) and duration of fragmented electrogram (d-Frag). A positive correlation was observed between changes in orthodromic conduction time and VT cycle length **(top).** However, the change in duration of the fragmented activities at the exit was not correlated with changes in VT cycle length **(bottom).**

lated with that in orthodromic conduction time, as shown in Fig. 4 ($r = 0.95$, $p < 0.001$).

Effect of mexiletine on local electrogram. The site of the earliest activation of VT showed abnormal results on the electrogram: 1.2 ± 0.6-mV amplitude and 146 ± 50-ms duration (Fig. 2 and 3). Pacing during sinus rhythm at this site resulted in a QRS configuration identical to that of VT, whereas pacing during VT resulted in acceleration in response to the pacing rate without any change in the QRS configuration.

After administration of mexiletine, the duration of the local electrogram during VT was prolonged to 176 ± 56 ms ($p <$ 0.001; mean change 23 ± 8%). However, electrogram prolongation was not correlated with prolongation of VT cycle length (Fig. 4). The mexiletine-induced change in duration of the local electrogram was not significant when measured during sinus rhythm (124 ± 54 vs. 125 ± 54 ms).

The pacing site showed normal electrograms (3.8 ± 0.9-mV amplitude, 52 ± 8-msec duration), and they showed little change after administration of mexiletine during VT as well as during sinus rhythm (53 ± 8 ms).

Effect of mexiletine on local conduction time and QRS duration. During VT, the local conduction time from the exit to the pacing site was 55 ± 26 ms and changed little after administration of mexiletine (58 ± 22 ms, p = NS). During VT, QRS duration was 154 ± 26 ms in the control state and was prolonged to 161 ± 27 ms after mexiletine; the change was small (4 ± 3%) but statistically significant ($p < 0.05$). During sinus rhythm, QRS duration showed little change (120 ± 48 vs. 127 ± 55 ms, p = NS).

Effect of antiarrhythmic drugs on effective refractory period. The effective refractory period was 240 ± 21 and 253 ± 12 ms at the pacing site and at the site of VT origin, respectively and did not change significantly after administration of mexiletine (238 ± 22 and 245 ± 11 ms, respectively, p = NS).

Discussion

Mechanism of VT. All VT in the present study was initiated and terminated with electrical stimulation and, furthermore, VT could be entrained with rapid ventricular pacing (11,12,17,18). When VT was interrupted at a critical paced cycle length, the site of the earliest activation was activated from a different direction and at a shorter timing, which suggests the presence of slow conduction (18). All these findings strongly suggest that the mechanism of VT is reentry.

Although some patients in the present study had VT unrelated to coronary disease, the mechanism of VT is most likely reentry with an excitable gap (19,20).

Action of mexiletine on central common pathway. Because mexiletine was administered after termination of VT, we did not determine whether mexiletine was able to terminate VT. Therefore, we described the electrophysiologic effects in VT in cases where mexiletine did not produce any antiarrhythmic response, and we did not attempt to explain the mechanism by which mexiletine might terminate VT or prevent induction in patients with that response.

The action of antiarrhythmic agents on the central common pathway may be assessed indirectly by observing changes in VT cycle length or more directly by changes in orthodromic conduction time during transient entrainment of VT (Fig. 1).

Kay et al. (3) observed a correlation between changes in VT cycle length and that of orthodromic conduction time to the exit of VT before and after the administration of procainamide, but such was not observed between the VT cycle length and the direct (antidromic) conduction time to the exit. This finding was interpreted to represent a preferential action of procainamide on the slow pathway of the reentrant circuit. A similar finding was observed using mexiletine in the present study, and a preferential action of the drug on the central common pathway was shown.

Mexiletine and local electrogram. The site at which VT originates has been shown (21,22) to consist of viable myocardium with poor cell to cell coupling, the basis for slow conduction (23,24), and such sites might show abnormal results on electrograms (12,23).

Class Ia antiarrhythmic agents have been shown to prolong the duration of the fragmented electrogram recorded during electrophysiologic study (1) or to prolong the late potential in the signal-averaging surface electrocardiogram (4), but the effect of class Ib agents has been shown to be negligible. In the present study, significant prolongation was observed in the electrogram of the diseased myocardium (at the exit), but not in the normal myocardium (the pacing site), after administration of mexiletine.

The different results between our study and previous studies (1,4) may be partly due to the fact that we measured the mexiletine-induced changes during VT at higher rates, whereas previous investigators studied the effects of mexiletine during sinus rhythm (1,4). Because of the fast kinetics of mexiletine, drug-induced changes might be negligible at lower rates (6–8,25).

Mexiletine prolonged the duration of the fragmented electrogram, but the change was not correlated with that of the VT cycle length. This finding might suggest that the property of the central common pathway is not homogeneous.

Limitations of the study. The small number of patients and the varying underlying heart disease were limitations. However, all VTs were entrained and interrupted at a critical paced cycle length with rapid ventricular pacing, and mechanism is most likely reentry with an excitable gap.

Conduction time through the normal myocardium is included in the orthodromic conduction time (a + b in Fig. 1), and the exit might contain some diseased tissue, which would affect local conduction time (c in Fig. 1). However, the latter changed little, and the change in VT cycle length or orthodromic conduction time caused by mexiletine was greater and must be due to changes in the central common pathway.

Due to slowing of the VT rate by mexiletine, some variables were not measured at exactly the same rate, but it seems unlikely that we overestimated the drug-induced changes in orthodromic conduction time or duration of fragmented electrograms. These changes would have been greater had we compared them at the same rate.

Conclusions. Significant prolongation was observed in VT cycle length and orthodromic conduction time through the central common pathway after the administration of mexiletine. These changes were highly correlated. However, local conduction time through the presumed normal myocardium and QRS duration showed little change. From these findings, a preferential action of mexiletine on diseased myocardium close to the central common pathway was suggested but was revealed at a higher heart rate.

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